

**REMARKS**

Reconsideration and withdrawal of the rejections set forth in the Office action dated June 8, 2011 are respectfully requested. Claims 1-6 are pending and claims 7-14 are withdrawn.

**I. Amendments**

Claim 1 is amended in accord with the Examiner's kind suggestion. Claim 1 is further amended to clarify the method steps. Basis for these amendments can be found, for example, on page 12, lines 17-20 and page 16, lines 17-21.

No new matter is added by way of these amendments.

**II. Claim Objections**

Claims 1-6 are objected to for alleged informalities. Applicants have amended claim 1 to recite "a sequence encoding for an extracellular domain" as suggested by the Examiner to improve the format of claim 1. Accordingly, Applicants respectfully request withdrawal of the objections to the claims.

**III. Claim Rejections Under 35 U.S.C. § 112, second paragraph**

Claim 5 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically the Examiner objected to the language "said signal sequence is an epidermal growth factor signal sequence" because the metes and bounds "of said signal sequence and/or EGF signal sequence is wholly unclear since said signal can be any biological signal related to any epidermal growth factor" (Office action page 4). The Examiner is reminded that the claim 5 refers to an epidermal growth factor signal *sequence* rather than an epidermal growth factor signal.

The Office recently provided supplementary examination guidelines for examination of claims in compliance with 35 U.S.C. §112, second paragraph (Federal Register, Vol. 76, No. 27, February 9, 2011). According to the guidelines, an indefiniteness rejection is appropriate where "a person of ordinary skill in the relevant art would read it with more than one reasonable interpretation." This is not the case with the present claims. A person of ordinary skill in the relevant art would understand

the present language to refer only to a signal sequence that is an epidermal growth factor sequence as explicitly stated in claim 5.

Here, the Examiner appears to be objecting to the breadth of the claim since the Action states that the language is "wholly unclear since said signal can be any biological signal related to any epidermal growth factor" (Office Action page 4). Such an objection is not the proper application of a rejection under 35 U.S.C. §112, second paragraph. As explicitly cautioned in the examination guidelines, "Examiners, however, are cautioned against confusing claim breadth with claim indefiniteness." A broad claim is not indefinite merely because it encompasses a wide scope of subject matter provided the scope is clearly defined. Instead, a claim is indefinite when the boundaries of the protected subject matter are not clearly delineated and the scope is unclear." Here, the scope of "said signal sequence is an epidermal growth factor signal sequence" is definite in that the one skilled in the art would understand the boundaries of the signal sequence as being an epidermal growth factor signal sequence.

Further, Examiner's reference to the function of the signal sequence does not clarify the rejection. The metes and bounds of the signal sequence are clear to one of skill in the art - the signal sequence is an epidermal growth factor signal sequence. A signal sequence has the known function of secretion of EGF as noted in the instant specification. The additional functions listed by the Examiner appear to be related to signal pathways, not a signal sequence.

In view of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

IV. Claim Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-6 were rejected under 35 U.S.C. § 112, first paragraph, written description, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6 were rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, allegedly because the prior art and instant specification do not disclose any direction or guidance to make a fusion protein containing an EGF signal sequence

and use for directing its fused partner to be exported outside the recombinant host cell once the fusion protein is produced by recombinant biotechnology. The Examiner contends that it is unpredictable to make and use the claimed nucleic acid encoding any EGF signal sequence as a signal sequence.

These rejections are respectfully traversed.

A. Written Description

The Examiner asserts that the prior art and instant specification fails to disclose a single example of a secretion signal sequence from a native EGF peptide sequence and having the function of directing a fused partner to be exported outside the recombinant host cell once the fusion protein is produced by recombinant technology (Office action , pages 5-6).

The essential purpose of the written description requirement is to show the possession of the invention as of the filing date as a *prima facie* date of invention. *In re Smith*, 481 F.2d 910, 178 U.S.P.Q. 620, 623 (CCPA 1973). Accordingly, the specification is required to contain a statement that adequately describes the invention as claimed. Considerations for this determination include (a) whether there was an actual reduction to practice; (b) the disclosure of drawings or structural chemical formulas; (c) the presence of sufficient relevant identifying characteristics; (d) the method of making the claimed invention; (e) the level of skill and knowledge in the art; and the predictability in the art. Relevant identifying characteristics include complete and/or partial structure; physical and/or chemical properties; and functional characteristics when coupled with a known or disclosed correlation between structure and function (see the USPTO's "Written Description Training Materials" Revision 1 March 25, 2008).

*The specification describes an actual reduction to practice*

Applicants first direct the Examiner to page 9, line 34 to page 10, line 5, for example, where Applicants clearly state the signal sequence may be an epidermal growth factor and that it is secreted. Example 1 describes an actual reduction to practice of an expression vector as claimed using an Igv leader sequence.

*The specification includes a relevant drawing*

Fig. 1A shows a map of an exemplary expression vector, which one skilled in the art would readily understand how to use in combining the claimed sequences. The map shows a sequence encoding an Ig<sub>v</sub> leader sequence. One skilled in the art would readily be able to substitute the Ig<sub>v</sub> leader sequence for a sequence encoding a different sequence encoding a signal polypeptide sequence such as an epidermal growth factor signal sequence. The expression vector shown (pYBS101) is actually a modification of the pcDNA3(+) expression vector commercially available from Invitrogen (see page 18, line 3).

*The level of skill and knowledge in the art is high*

One skilled in the art would have an advanced degree in molecular biology, or similar field, and would be well versed in molecular biology processes and techniques including preparation of expression vectors. One skilled in the art would also be familiar with the literature and tools relating to molecular biology. One skilled in the art would also have the technical skills needed to practice the experimentation described in the scientific literature relating to expression vectors and the sequences included within the vectors.

*The predictability of signal sequences and substituting signal sequences in an expression vector is high*

Predicting the signal sequence of a known protein sequence was well within the skill of one in the art and highly predictable by analysis of possible cleavage sites. Programs are available to predict the presence and location of signal peptide cleavage sites and therefore predict the signal sequence (e.g. the SignalP and Phobius programs). Particular signal peptides are widely available such as in the SPDb database (<http://proline.bic.nus.edu.sg/spdb/index.html>). Thus, predicting the signal sequence of a known protein sequence is highly predictable.

The level of skill and knowledge in the art was such that those skilled in the art knew of numerous EGF signal sequences that could be used in the present method to target the expressed protein to the cell surface. Although these additional sequences are not disclosed in the present specification, a patent application is not required to reproduce knowledge that is available in the art. Such sequences are widely available in the NCBI Genbank online sequence database ([www.ncbi.nlm.nih.gov/gquery/](http://www.ncbi.nlm.nih.gov/gquery/)).

Based on these factors, one of ordinary skill in the art of molecular biology would recognize the inventors to have been in possession of the claimed method at the time of filing. Withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification at the time of filing is respectfully requested.

**B. Enablement**

Claims 1-6 were rejected as allegedly not enabled. Specifically, these claims are rejected for the recitation "wherein said signal sequence is epidermal growth factor signal sequence" in claim 5 (Office Action page 6). Claims 1-4 and 6 are included in the rejection since they contain the scope of claim 5.

The enablement requirement of § 112 is satisfied when the specification describes the claimed invention in a manner that permits one of skill in the art to make and use the invention without undue experimentation. That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is undue (see, for example, *In re Vaeck*, 20 USPQ 1438 (Fed. Cir. 1991) and MPEP § 2164.01). Even complex experimentation is not undue if the art typically engages in such experimentation (MPEP § 2164.01). The amount of guidance or direction needed to satisfy the enablement requirement is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. (MPEP § 2164.03). Thus, the question of enablement is one of predictability in view of what is known in the art.

Applicants respectfully submit that the experimentation required to practice the method of claim 5 is not undue.

In determining enablement and whether any necessary experimentation is undue, the courts have identified several Wands factors to be considered:

*(i) The breadth of the claims and (ii) nature of the invention:* Claim 5 relates to the specific embodiment wherein the signal sequence is an epidermal growth factor signal sequence.

*(iii) The state of the prior art, (iv) level of ordinary skill in the art, and (v) the predictability of the art:* Epidermal growth factor was well known in the art as acknowledged by the Examiner (Office Action page 6). Further, determining the signal sequence of any epidermal growth factor sequence was routine to one skilled in the art.

at the time of filing of the present application. As described in the Kingman *et al.* reference, used by the Examiner in the prior art rejections below, the state of the art was such that signal sequences were known to have the function of localizing a protein expressed by transfected cells to the surface of the cell (page 17, lines 20-23). Further, as described by Kingman *et al.*, heterologous signal sequences were known and typical (page 17, lines 15-18). Identification of a signal sequence for a known protein was known and the SignalP program was available to predict the signal sequence based on the presence of cleavage sites (see page 18, lines 15-19).

The level of skill in the art was high as one skilled in the art would generally have an advanced degree in molecular biology, or a similar field. One skilled in the art would be familiar with the art relating to molecular biology and to making and using expression vectors, in particular. The skilled artisan would also have the technical skills needed to practice the experimentation described in the scientific literature relating to expression vectors and the sequences included within the vectors.

*(vi) The amount of direction or guidance presented and (vii) the presence or absence of working examples:* The specification discloses that the signal sequence targets the expressed protein to the cell surface and that an example of a secreted protein containing a suitable signal sequence is the epidermal growth factor protein sequence (page 10, lines 3-5). Example 1 provides a working example of the method using an Igk signal sequence.

*(viii) The quantity of experimentation necessary:* The method of claim 5 is directed to a method that involves preparing an expression vector that includes an epidermal growth factor signal sequence. The epidermal growth factor peptide was well characterized and means were available to predict the signal sequence (e.g. SignalP). One skilled in the art would have the skills to include a heterologous signal sequence in an expression vector.

Thus, the present application in view of the knowledge of one skilled in the art provides ample guidance for any experimentation necessary in the present method. (MPEP § 2164.01(a), citing *in re Wands*, 858 F.2d 731,737 (Fed. Cir. 1988)).

In light of the above, Applicants submit that one of ordinary skill in the art would readily be able to make and use the claimed method, despite any experimentation that

might be required. Applicants further submit that this conclusion is supported by the fact that the majority of the Wands factors favor enablement. Accordingly, Applicants respectfully request that the rejections be withdrawn.

V. Claim Rejections Under 35 USC § 102

Claims 1 and 4 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by *Kingsman et al.* (PCT Publication No. WO 03/089649).

Claims 1-4 and 6 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by *Fayen et al.* (Methods in Enzymology, 2000, 327:351-368).

These rejections are respectfully traversed.

A. The Present Claims

Independent claim 1 is directed to a method of generating tethered extracellular domains of transmembrane proteins. The method comprises preparing an expression vector comprising a 5' nucleic acid sequence encoding a signal polypeptide sequence, a nucleic acid encoding a purification epitope tag polypeptide, a sequence coding for an extracellular domain of a membrane protein, and a 3' nucleic acid encoding an anchor polypeptide sequence. Mammalian cells are transfected with the expression vector to generate an anchor tethered protein targeted to an extracellular domain of a plasma membrane. The anchor tethered protein is displayed on a lipid bilayer array where the displayed anchor tethered protein is capable of binding to a ligand.

B. The Cited Art

Kingsman et al. relate to an expression vector comprising an amino-terminal tag sequence and a signal sequence operably linked to a nucleotide of interest (Abstract). The amino-terminal tag sequence is inserted between the signal sequence and the nucleotide sequence of interest (page 1, lines 7-9). The utility of the nucleotide sequence of interest is determined by transfected a host cell with the expression vector, selecting for host cells expression the sequence, and determining the expression profile of the protein expressed from the nucleotide sequence of interest (page 4, lines 20-25). The expression profile of the protein can be used to determine whether the nucleotide sequence of interest is a disease target for use in cancer

immunotherapy (page 3, lines 29-31). The nucleotide sequence is preferably a tumor associated antigen.

Fayen et al. describe engineering proteins bearing C-terminal GPI anchors in place of their normal transmembrane and intracellular sequences for incorporation into cell surface membranes (page 353, lines 4-6 and 16-18). Cells may be transfected with the cDNA encoding the GPI-modified protein and the modified protein (page 360, lines 3-5. The cDNA may be ligated into an expression vector (page 362, lines 6-7). The GPI-modified protein may be purified and incorporated into cells.

### C. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131.

Kingsman *et al.* and Fayen *et al.* each fail to teach at least a method including the step of *displaying the anchor tethered protein on a lipid bilayer array*. Kingsman *et al.* teach their method may be used for screening using phage display techniques or transformed host cells (pages 56-57). Fayen *et al.* teach anchoring GPI-anchored proteins into cells (page 353, lines 7-8 and page 361, lines 19-22).

As neither Kingsman *et al.* nor Fayen *et al.* teach each and every element of the claimed method, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §102.

### VI. Claim Rejections Under 35 USC § 103

Claims 1, 3 and 4 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kingsman *et al.* (WO 03/089649; Published Oct. 30, 2003; as cited in the IDS) in view of Groves *et al.* (US Patent Publication No. 2002/0160505, hereafter "Groves I"), Groves *et al.* (Science, 1997, 275:651-653, hereafter "Groves II"), Cooper (Nature Reviews Drug Discovery, 2002, 1: 515-528) and McCarthy *et al.* (US Patent No. 6,391 ,586).

Claims 1-4 and 6 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Fayen *et al.* in view of Groves I, Groves II, Cooper, and McCarthy *et al.*

A. The Present Claims are described above.

B. The Applied Art

Kingsman et al. is described above.

Fayen et al. is described above.

Groves I relates to patterned lipid membranes doped with various components to modulate cell adhesion. Suitable dopants include an "impurity" in the lipid composition (preferably phosphatidylserine lipid), a protein that modulates cell adhesion, and a chemical moiety that chemically binds to a certain type of cell.

Groves II describes micropatterning of lipid bilayers on solid supports. The bilayers are formed by fusion of small unilamellar vesicles which can include incorporation of membrane proteins.

Cooper relates to optical biosensors to analyze biomolecular interactions. For use with the biosensor, lipid bilayers can be "bound to, but structurally de-coupled from the solid support" by the use of flexible polymer cushions.

McCarthy et al. describe methods for identifying genes encoding novel proteins. The methods include inserting cDNA from a randomly primed library into a mammalian expression vector adjacent a cDNA encoding placental alkaline phosphatase (AP) which lacks a secretory signal. In this manner, the presence or absence of AP in the supernatant of transformed cells indicates a signal sequence in the cDNA of interest.

### C. Analysis

Determining obviousness under 35 U.S.C. § 103(a) requires an objective analysis involving four factual inquiries, which include:

- (a) determining the scope and content of the prior art;
- (b) ascertaining the differences between the prior art and the claims in issue;
- (c) resolving the level of ordinary skill in the art; and
- (d) evaluating evidence of secondary considerations.

See *Graham v. John Deere*, 383 US 17, 18, 148 USPQ 459, 467 (1966); see also M.P.E.P. § 2141.

When determining whether a claim is obvious, an examiner must make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis

added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (*citing In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). Moreover, the Supreme Court recently stated, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

C1. Rejection over Kingsman *et al.* in view of Groves I, Groves II, Cooper, and McCarthy *et al.*

*The claimed method is more than the predictable use of prior art elements according to their established functions*

Display of an expressed, anchored sequence on a non-native, lipid bilayer array is not predictable from the teaching of the cited references. As noted above, Kingsman *et al.* teach an expression vector comprising an amino-terminal tag sequence and a signal sequence operably linked to a nucleotide sequence of interest to establish the cellular location of a cDNA gene product (Abstract and page 4, lines 4-5). When a host cell is transfected with the expression vector, the cDNA gene product is *expressed in the host cell*. The cellular location of the protein expressed is identified with an expression profile. For the membrane proteins, the host cell's native membrane provides for proper presentation of the protein. A native membrane has numerous components in the membrane, each affecting characteristics of the lipids that would in turn affect the confirmation of macromolecules embedded in or associated with the membrane. This complex composition is not present in the lipid bilayer array of the present method.

It is well known that proper folding of membrane proteins within the native cellular environment is a very complex process. One of ordinary skill in the art would not expect proper folding of membrane proteins merely by mixing a recombinantly expressed protein with a lipid bilayer array in the absence of all the cellular components normally recognized as necessary for proper protein presentation.

C2. Rejection over FAYEN et al. in view of GROVES I, GROVES II, COOPER, and MCCARTHY et al.

*The claimed method is more than the predictable use of prior art elements according to their established functions*

Display of an expressed, anchored sequence on a non-native, lipid bilayer array is not predictable from the teaching of the cited references. As noted above, FAYEN et al. teach engineering proteins bearing C-terminal GPI anchors in place of their normal transmembrane and intracellular sequences. The expressed proteins are purified and inserted into *native* cell membranes of intact cells. FAYEN et al. teach these native membranes are required for proper incorporation of the GPI-anchored proteins (page 368, lines 3-13, citations not included):

Reincorporated GPI-anchored proteins, like their naturally synthesized counterparts, transit slowly from the site of their membrane insertion into detergent-insoluble, cholesterol-rich membrane rafts that comprise, in some cells, caveolar membrane microdomains. Kinetic analyses have shown that the transit to these membrane microdomains progressively increases for 24 hr after membrane reinsertion. Some of the complex intracellular properties associated with GPI-anchored proteins, including their ability to participate in intracellular signaling, require transit into these specialized membrane microdomains. The full reconstitution of the properties of reincorporated GPI-modified proteins is thus not complete until this transition has occurred.

As acknowledged by FAYEN et al., the host cell's native membrane provides for and is required for proper presentation of the protein. Nor does the teaching in any of the cited GROVES I, GROVES II, COOPER, or MCCARTHY et al. provide an expectation that an expressed, anchored protein targeted to an extracellular domain displayed on a lipid bilayer array would be expected to function properly.

Applicants have unexpectedly shown that a synthetic lipid bilayer array displaying an anchor tethered protein is functional. As described in Example 10, human B7-1 and human ICAM-1 anchor tethered proteins displayed on a bilayer array as claimed were functional to bind Jurkat T cells.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

VII. Conclusion

Applicants believe that the pending claims are in condition for Allowance. A Notice of Allowance is therefore respectfully requested.

If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at 650-590-1939.

The Commissioner is hereby authorized to charge any additional fees deemed to be due with the filing of this communication to Deposit Account No. 50-4616.

Respectfully submitted,  
King & Spalding LLP

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